

# BMJ Open Prevalence of depression, stress and suicide tendency among individuals with long COVID and determinants: a protocol of a systematic review and meta-analysis

Razieh Bidhendi-Yarandi,<sup>1,2</sup> Akbar Biglarian,<sup>3</sup> Enayatollah Bakhshi,<sup>2</sup> Mohammad-Reza Khodaei-Ardakani,<sup>4</sup> Samira Behboudi-Gandevani <sup>5</sup>

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For numbered affiliations see end of article.

## Correspondence to

Dr Samira Behboudi-Gandevani; samira.behboudi-gandevani@nord.no

## ABSTRACT

**Background** It is well known that the COVID-19 pandemic has had a devastating impact on mental health, especially among individuals with long COVID. This systematic review and meta-analysis aims to investigate the prevalence of depression, stress and suicide tendencies among individuals with long COVID, as well as to explore the factors that contribute to these conditions.

**Methods and analysis** A comprehensive review of literature will be conducted in various databases of including PubMed, including Medline, Embase, PsycINFO, CINAHL and Cochrane Library. The studies to be included in this review will be published in the English language, and the time frame of included studies will be from the date of inception of COVID-19 until 30 December 2023. Two independent reviewers will identify studies for inclusion based on a screening questionnaire, and the JBI standardised critical appraisal checklist for studies reporting prevalence data will be used to assess the methodological quality. The strength of the body of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation approach. To analyse the data, a robust Bayesian approach will be applied using the STATA software package (V.14; STATA) and JASP software. The findings of this systematic review and meta-analysis will provide valuable insights into the prevalence of depression, stress and suicide tendencies among individuals with long COVID, as well as the factors that contribute to these conditions.

**Ethics and dissemination** There is no research ethics board approval required. The dissemination plan is to publish results in a peer-reviewed academic journal. **PROSPERO registration number** CRD42022346858.

## INTRODUCTION

The COVID-19 pandemic, considered a natural catastrophe of the century, has a devastating impact on the global community.<sup>1</sup> According to the WHO, the COVID-19 pandemic has affected over 750 million

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study will report the prevalence of depression, stress and suicide tendencies among individuals with long COVID.
- ⇒ The study will assess a large number of variables that may contribute as determinants.
- ⇒ The broad search strategy, using various databases should help ensure that all relevant literature is included.
- ⇒ The literature will be carefully assessed for quality using the Joanna Briggs institute (JBI's) critical appraisal tools and Grading of Recommendations Assessment, Development and Evaluation approach.
- ⇒ The main limitation of the individual participant data meta analysis (IPD-MA) will be the difficulty in obtaining data sets from the authors as well as the heterogeneity of the data sets and possible publication bias.

individuals worldwide and resulted in nearly 7 million deaths.<sup>2</sup>

While the majority of infected patients either remain asymptomatic or display mild symptoms,<sup>3</sup> approximately 20% of patients experience a severe form of the disease characterised by clinical manifestations such as acute respiratory distress syndrome and a severe immune response.<sup>4</sup> Furthermore, it has been observed that over 30% of individuals affected by COVID-19, regardless of the initial severity of their illness, continue to experience persistent and prolonged symptoms, and may even develop new ones, after recovery.<sup>5,6</sup> This condition is commonly referred to as post-COVID-19 syndrome or long COVID. Although recognised by institutions such as the National Institute for Health and Care Excellence,<sup>7</sup> the Centers for Disease Control and Prevention,<sup>8</sup> and the WHO,<sup>9</sup> a

universally accepted definition for this phenomenon has not yet been established.

Emerging evidence has reported the long-term neuropsychiatric sequelae of COVID-19, including depressive symptoms, fatigue, anxiety and cognitive impairment, along with other enduring neuropsychiatric symptoms such as anosmia, ageusia, dizziness, headache, seizures and physical manifestations.<sup>10–15</sup>

In this respect, it is suggested that COVID-19 may effect on the central nervous system due to the neurotropism of the virus, the hyperinflammatory state and hypercoagulability following infection, particularly in severe cases.<sup>16–18</sup> Additionally, experiencing a severe illness or an acute onset of such an illness can be a traumatic event.<sup>18</sup> Furthermore, studies have indicated that the isolation precautions implemented for infection prevention have been linked to severe mental health issues.<sup>19</sup>

However, depression, anxiety and higher stress levels have become significant contributors to the global health burden and are expected to have long-term economic and social consequences.<sup>20,21</sup> The incidence of depressive symptoms, based on various post-COVID-19 follow-ups, is reported to range between 20% and 40%.<sup>13,22</sup> Additionally, individuals who identify as female and those who had a pre-existing psychiatric disorder before COVID-19 are at an elevated risk of experiencing post-COVID-19 fatigue.

The COVID-19 pandemic has also led to a significant increase in stress levels for the majority of people, with 11% reporting the highest levels of stress during the early stages of the pandemic. Social support has been identified as a protective factor against stress, particularly during lockdown periods. Factors such as being female and facing financial problems have shown the largest effect on escalating stress levels. Additionally, psychological flexibility, mindfulness and education have emerged as significant protective factors.<sup>23</sup>

Furthermore, there is evidence indicating a high probability of suicidal ideation and tendencies within this patient population, attributed to symptoms of psychiatric, neurological and physical illnesses, as well as the experience of physical and social isolation.<sup>24,25</sup>

However, there is still a lack of comprehensive evaluations regarding the prevalence and determinants of certain neuropsychiatric sequelae, such as depression, stress and suicide tendencies, among individuals with long COVID. Assessing the methodological quality of studies is crucial in determining the transferability of results and identifying research gaps. To address this challenge, a recent systematic review and meta-analysis will be conducted. This current systematic review and meta-analysis aims to investigate the prevalence of depression, stress and suicide tendencies among individuals with long COVID after 12 weeks following their initial COVID-19 infection. In addition, this study sought to address significant determinants of mental health issues.

## METHODS AND ANALYSIS

### Study registration

This study adheres to the assessment of multiple systematic reviews tool and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (online supplemental file 1).<sup>26</sup> The protocol of this study was registered in PROSPERO (CRD42022346858).

The review strategy was framed based on the Population, Intervention/Exposure, Comparator and Outcomes statement as follows: P: Individuals with long COVID after 12 weeks following COVID-19 infection. E: COVID-19, C: None specified and O: The primary outcome of the study is the number, prevalence or incidence of reported stress, depression and suicide tendency and their determinants in individuals with long COVID. Secondary outcomes as insomnia and anxiety will considered as well.

### Eligibility criteria

Types of studies: We will include peer-reviewed observational studies published in the English language and report the outcome of interest in individuals with long COVID, as well as their determinants, regardless of the primary observational study design. This includes longitudinal cohort, cross-sectional and case-control studies.

Types of participants: We will include individuals with a confirmed diagnosis of COVID-19 who had new and/or persistent signs and symptoms more than 12 weeks following COVID-19 infection and did not exclude any studies based on gender, ethnicity, disease severity or setting.

Types of outcome measures: The number, prevalence or incidence of reported stress, depression and suicide tendency in individuals with long COVID, as well as their determinants, using validated screening tools.

### Inclusion and exclusion criteria

Exclusion criteria will be non-original studies including reviews, commentaries, editorials, letters, case reports, conference proceedings and books, original studies without accurate and clear data on research variables and duplicated data.

### Search strategy

We will perform a comprehensive review of literature in various databases of PubMed [NCBI] including MEDLINE [Ovid], Embase [Elsevier], PsycINFO [APA], CINAHL [EBSCOhost] and Cochrane library [Cochrane Library] (online supplemental table 1). Additionally, we will conduct a manual search in the references list of selected studies and other relevant papers and previous reviews to ensure we identify all eligible studies. We will use a combination of Medical Subject Headings terms and other keywords to retrieve the articles.

### Language and time frame

Studies to be included will be published in English. The time frame of included studies will be from the date of inception of COVID-19 until 30 December 2023.

### Study selection and data extraction

The titles, abstracts and full texts of selected studies were screened independently by two authors (SB-G and RB-Y) based on the eligibility criteria, and the following data will be extracted from eligible studies. Any disagreement will be discussed with a third member of the review team and decisions will be documented. In the case of missing information concerning the outcomes of interest, we will directly contact study authors up to three times to obtain additional information. The following data will be extracted from all the studies meeting the inclusion criteria: first author's last name, name and email of the corresponding author and of other authors if present, publication year, country, study design, sample size, population and its characteristics, setting and data source, period of assessment (years), outcome measurements, list of covariates included in design and analysis.

In the case of overlapping studies (published on the same data source), we will use the most recently published results, or the largest sample size, or we will evaluate the study case by case. To avoid the risk of overlapping studies for each study, we will extract: (a) the names of the authors and (b) the names of the databases/studies

(Data source) and we will check for duplicates; then, in the case of doubts, we will directly contact the authors.

The accuracy of data before the meta-analysis will be assessed by double-checking the data extraction process to ensure no bias in the data extraction and data entry. Any discrepancies will be resolved by discussion and the third review author.

### Assessment of methodological quality

Standardised critical appraisal instruments for prevalence studies such as, JBI's critical appraisal tools, will be used for methodological quality assessment of eligible studies. The JBI critical appraisal checklist for prevalence studies having nine checklist items. Articles with an overall quality assessment score of greater than half (50%) considered as moderate to high quality.<sup>27</sup>

Two independent reviewers (SB-G and RB-Y) will critically appraise the included studies, and any discrepancies will be resolved by discussion and the third review author (AB).

Additionally, we will employ the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to evaluate the level of certainty of evidence for each outcome. The GRADE approach involves assessing various factors, including risk of bias (limitations in study design and execution), inconsistency (or heterogeneity), indirectness (population, intervention, comparison and outcome, as well as applicability), imprecision (number of events and CI) and publication bias.<sup>28</sup> Based on the GRADE methodology, the certainty of evidence will be categorised as follows: high (further research is highly unlikely to alter our confidence in the estimated effect), moderate (further research is likely to significantly impact our confidence in the estimated effect and may lead to a change in the estimate), low (further

research is highly likely to significantly impact our confidence in the estimated effect and is likely to result in a change in the estimate) or very low (the estimated effect is highly uncertain).

### Statistical analysis

The STATA software package (V.14; STATA) and JASP software will be used to conduct statistical analysis. Heterogeneity will be evaluated using the  $\chi^2$  test and  $I^2$  index. Publication bias will be assessed using funnel plots and statistical tests. In case of significant results, the robust Bayesian approach will be applied. The random effect model will be used for the estimation of the pooled prevalence via the meta-prop method with a pooled estimate after Freeman-Tukey double arcsine transformation to stabilise the variances. Forest plots for each outcome and by any extracted subgroups, such as gender, regions, severity of the disease and etc, will be illustrated as well. Meta-regression analysis will be run to assess the effect of extracted determinants as the potential sources of heterogeneity. Sensitivity analysis will be applied to find influential studies in case. The strength of the body of evidence will be assessed using the GRADE approach.

If we are unable to conduct meta-analyses, we plan to conduct a narrative synthesis to report the prevalence and risk factors for each outcome of interest assessed and if there were any patterns or gaps in the literature.

### Patient and public involvement

Patients and the public were not involved in the study design.

### DISCUSSION

The mental health and psychological well-being of people worldwide were greatly affected by the COVID-19 pandemic. Besides the physical health consequences and mortalities resulting from the virus, efforts to contain the spread of COVID-19 introduced significant challenges in people's lives, such as unemployment, financial difficulties, reduced social interactions and instances of homelessness.<sup>29</sup> Nevertheless, an increasing amount of evidence has indicated that individuals who have recovered from COVID-19 may encounter enduring symptoms that impact various organ systems beyond the initial acute stage of the infection, which is commonly referred to as long-COVID.<sup>30</sup> However, no previous systematic review and meta-analysis has focused on long-term persistent or new symptoms of mental health disturbances in individual with long COVID, and it remains unclear to which kind of risk factors and determinants could be affected on them after 12 weeks of postinfection. With the emerging data of longer-term follow-up of COVID-19 patients, it is important to investigate whether the spectrum of long-lasting depression, stress and suicide tendency in these patients.

We will seek to systematically synthesise existing evidence on long COVID. We will estimate the pooled



prevalence and also will summarise potential risk factors for depression, stress and suicide tendency in individuals with long COVID.

### Strengths and limitations of this study

The strength of our study would be, first, the high quality of evidence that is produced. To our knowledge, these will be one of the pioneer systematic review/meta-analysis investigating the prevalence and determinants of mental health disturbances in individual with long covid. The robust Bayesian meta-analysis will be applied in case of existence of publication bias which is an important mythological issue in the meta-analysis of prevalence.<sup>30</sup> The main limitation of the study will be the paucity of studies assessing outcomes in long-covid and also the lack of access to the full text of the articles, which will be solved by correspondence with the author. In addition, strong heterogeneity may be existed among studies which will be considered using random effect model or proper subgroup analysis.

### Ethics and dissemination

There is no research ethics board approval required. The dissemination plan is to publish results in a peer-reviewed academic journal.

### Author affiliations

<sup>1</sup>Social Determinants of Health Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

<sup>2</sup>Department of Biostatistics and Epidemiology, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

<sup>3</sup>Social Determinants of Health Research Center, University of Social Welfare and Rehabilitation Science, Tehran, Iran (the Islamic Republic of)

<sup>4</sup>Razi Psychiatric Hospital, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

<sup>5</sup>Faculty of Nursing and Health Sciences, Nord University, Bodø, Norway

**Twitter** Mohammad-Reza Khodaei-Ardakani @kh.4518@yahoo.com

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### ORCID iD

Samira Behboudi-Gandevani <http://orcid.org/0000-0003-3526-640X>

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